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NOTES ON THE ESTIMATION OF NITROGLYCERINE.

By F. W. Heyl and J. F. Staley.

After abandoning the older nitrometer method for the control of nitroglycerine in pharmaceutical preparations, it was the practice in this laboratory during a considerable period to use in its place the modified Kjeldahl method wherever possible. The Kjeldahl method was found to give results in this instance fully as reliable as in the case of other highly nitrated organic substances such as picrates and picrolonates, which have thus been successfully analyzed.

Recently the latter method has been supplanted in this laboratory by that introduced by Scoville,[1] particularly when preparations bearing minute quantities are under examination. Before abandoning the Kjeldahl method for the superior method of Scoville, we first compared the results obtained by using these two methods in the routine analysis, upon various samples of nitroglycerine preparations. In view of the comparatively large number of collaborators who took part in the coöperative work recently described[2] in the annual report of the Official Agricultural Chemists, the results here given may be of some interest.

In this valuable bulletin the nitroglycerine found by the modified Scoville method is compared with results obtained gravimetrically upon the same sample by extracting with anhydrous ether. It was the experience of some of the collaborators that the gravimetric

[1] Amer. Jour. Pharm., 83, 359, 1911.
[2] *Bureau Chemistry U. S. Dept. Agric. Bull.*, 162, 214, 1912.

determination of nitroglycerine was inaccurate, and this would be even more liable to error in anything but the simplest preparations. It is, therefore, of interest to note the comparisons here given of nitroglycerine content as determined by the Scoville method and by the modified Kjeldahl.

Scoville [3] has already briefly compared these values and the figures here given lead to the same conclusions as his, *i.e.*, that the results obtained by these methods are quite alike, and that the variations are due to the difficulties of the methods.

For the analysis of tablets containing minute quantities there can be little doubt that the colorimetric method is both the easier and the more accurate. But in the case of the stock preparations such as the concentrated alcoholic solutions and triturations, the larger quantities of nitroglycerine under analysis make it possible to obtain closely agreeing results by the modified Kjeldahl method. The manufacturing processes can be closely controlled when the stock substances are standardized by the Kjeldahl and the finished product by the colorimetric method, particularly when the conditions are so standardized that a definitely known loss of nitroglycerine, previously determined, is allowed for. Such data are given in the table.

It will be observed, that under the conditions employed for manufacture, the losses of nitroglycerine involved have been reduced to quite narrow limits, averaging about five per cent for moulded tablets and about eleven per cent for compressed ones. Our findings on the compressed tablets are at variance with the losses previously recorded [4]; but this is due to the fact that the tablets are prepared by mixing dry granulations instead of attempting to granulate the mixture. A tablet prepared in this way neither discolors nor loses its strength, and there is no doubt but that a stable standard product results, at least as long as the preparation is properly preserved.

Experimental.

For the colorimetric analyses a method equivalent to that outlined in the report [5] of the Official Agricultural Chemists was employed.

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[3] *Loc. cit.*

[4] Amer. Jour. Pharm., 79, 555, 1907.

[5] *Loc. cit.*

The nitrogen determinations were made as follows: Approximately one gram of the ten per cent alcoholic solution was used for analysis. Where tablets and triturations were analyzed they were first extracted with anhydrous ether, and the ether extracts were evaporated to dryness under reduced pressure at room temperature. The residue was taken up in 1 to 2 c.c. alcohol and collected at the bottom of the flask. Upon this alcoholic solution one gram of salicylic acid was placed and then the Kjeldahl flask was cooled in a freezing mixture. Upon this 40 c.c. of the customary salicylic acid in sulphuric acid solution (previously chilled) was poured and then the mixture was allowed to warm to room temperature, with occasional agitation. The nitration mixture was reduced by the gradual addition of 2 grams of zinc dust, and then the reduction was completed by allowing the reaction to continue for six hours. The mixture was heated gently for five minutes, ten grams of potassium sulphate was added, and the Kjeldahl determination was then finished in the usual manner, using N/20 solutions.

The following table gives the results of analyses on tablets, some prepared experimentally and some commercially:

Preparation analyzed.	Nitroglycerine calculated gm. per tablet.	Found Kjeldahl.	Found Scoville.	Loss, per cent.
1. Nitroglycerine sol.	.....	9.83% 9.65% 9.66% 9.82%	9.75% 9.87%	
2. Nitroglycerine trit.	.....	9.56% 9.71% 9.99% 9.63%	10.03% 9.88%	
3. Compressed tablets	0.0007744	0.0007228 0.0007039	0.0007044 0.0006843 0.0007083	9.0 11.6 8.6
4. Compressed tablets	0.0005194	0.0004557 0.0004768 0.0004546	0.0004540 0.0004508	12.6 13.2
5. Compressed tablets	0.0007732	0.0007395	0.0007038 0.0006967 0.0006850	9.0 9.8 9.9
6. Compressed tablets	0.0006234	0.0005298 0.0005298	0.0005273 0.0005559 0.0005559	15.4 10.8 10.8
7. Compressed tablets	0.0004015	0.0003512 0.0003474	0.0003552 0.0003596	11.5 10.4
8. Moulded tablets	0.0006493	0.0006328 0.0006328	0.0006588	0.0
9. Moulded tablets	0.000658	0.0006280	0.000616*	6.8
10. Moulded tablets	0.0005351	0.0005237	0.0005085 0.0005184	4.9 3.2
11. Moulded tablets	0.000720	.....	0.0006836	5.0
12. Moulded tablets	0.000688	0.000629	0.0006480	5.9

* This analysis was made three months after the Kjeldahl.

Since the losses involved in the manufacture of these products must vary with the mechanical details, a brief description of the mechanical conditions employed will suffice. The compressed tablets were usually made in unit runs of 50,000 and the calculated strength in the table was found by taking into account both the waste, which was in each case weighed, and also the over or under run in number. The moulded tablets were made in unit batches of 15,000 and dried artificially in 45 to 60 minutes. All the calculations of loss are based on the colorimetric determinations.

Contribution from the Chemical Research
Laboratory of THE UPJOHN COMPANY.
KALAMAZOO, MICH., March, 1914.

THEORIES UNDERLYING THE USE OF ANTITOXINS AND VACCINES.*

BY A. PARKER HITCHENS, M.D., Glenolden, Pa.

The action of antitoxins has so definitely passed beyond the stage of pure speculation that I think there will be little difficulty in expounding the theories underlying their use. With regard to vaccines likewise we have come to understand more clearly their mode of action without the use of a terminology recognized only by the initiated few.

Out of studies in immunology—the science dealing with the mechanism of contagious diseases—have developed methods by which the body may be assisted either to prevent disease-producing germs from gaining a foothold, or to eliminate them after they have become established.

The disease-producing bacteria are classified in various ways, according to their functions. For our present purpose, the classification of most interest is that which considers the bacteria according to their manner of causing disease. Thus we find that one group of bacteria produces definite, soluble, and diffusible poisons, and that all the symptoms of the disease are directly or indirectly dependent on the action of these poisons upon the tissues for which they have an affinity. The second group of bacteria, on the contrary, does not produce soluble and diffusible toxins in appreciable

* Read at a meeting of the American Pharmaceutical Association, Philadelphia Branch, April 7, 1914.

quantity—their effect is brought about by a much more complicated process. We believe the production of disease by this class of bacteria is not a function in which they alone participate, but is the result of their interaction with the body cells.

Antitoxins.

Belonging to the first class of bacteria, the only organisms of interest to us are the *diphtheria* bacillus and the *tetanus* bacillus. These produce soluble and diffusible poisons—*toxins;* and spontaneous recovery from these diseases depends upon the generation by the tissues of a substance which will neutralize the toxins—*antitoxins.* The requisite antitoxins can be easily produced in animals and transferred to the bodies of patients by administering the blood serum of the treated animals.

For obvious reasons, horses are generally selected for the production of antitoxin. The germs in question are developed upon a fluid artificial culture medium—veal broth. After the bacteria are removed from the full-grown culture, the sterile filtrate, containing the specific toxins, is injected subcutaneously into the horses. The horses react by the production of antitoxin. Enormous quantities of toxin are administered, and consequently enormous quantities of antitoxin are generated and stored in the blood serum of the animal. The antitoxins on the market, then, consist of this blood serum, either native or chemically treated so that the pseudoglobulin constituent of horse serum which carries with it the antitoxic principle is removed and furnished, in solution, in as pure a state as possible.

The strength of the antitoxin is determined by titrating it against toxin, the guinea pig being used as indicator. In defining a unit at present, there is no more reason to say that it is the amount that will neutralize 200 fatal guinea-pig doses of a theoretically pure toxin than there is, in defining an inch, to say that it has a definite relation to the circumference of the earth. Twelve inches make 1 foot, 36 inches 1 yard; 1000 units of diphtheria antitoxin constitute the immunizing dose, 5000 units the average initial curative dose; 1500 units is the official immunizing dose of tetanus antitoxin.

The action of diphtheria antitoxin may be clearly illustrated by imagining the disease to be due to a mineral acid generated within the body and poured into the circulation in constantly increasing quantities. According to the urgency of the case, let us

inject a corresponding quantity of a harmless alkali. The acid is neutralized, the disease is controlled, and the fate of the patient now depends only upon the amount of damage done to the tissues before the alkali was administered.

In tetanus the case is slightly different. Tetanus toxin has a strong affinity for the nerve tissues, and the compound formed by this union cannot be split up by antitoxin. After symptoms of the disease have developed, there is but one hope in treating tetanus with antitoxin. If treatment has begun before the lethal quantity of toxin has been fixed by the nervous tissue, and if the amount of antitoxin then administered be sufficient to neutralize the free toxin in the blood, there is a chance that recovery may ensue.

Bacterial Vaccines.

For a clear understanding of the action of bacterial vaccines, it may be helpful to consider this subject from the standpoint of our knowledge of anaphylaxis. Anaphylaxis, in its derivation, means a lack of resistance—it is the opposite of prophylaxis. Richet, in his investigation of certain poisons derived from sea urchins, noted that an injection of this poison into a dog, instead of rendering the animal immune to a second dose, actually made him more susceptible. The work of Rosenau and Anderson showed still more clearly the operation of this phenomenon.

Anaphylaxis concerns the effect of proteins or albuminous substances upon animals; it concerns *all* proteins, whether they are poisonous in themselves or not; for instance, egg white and normal horse serum act precisely as the proteins of the plague bacillus or of the typhoid bacillus. And, furthermore, the proteins of dead bacteria act practically in the same way as the proteins of living bacteria. It must be remembered, however, that anaphylactic symptoms can be produced only by proteins foreign to the animal; that is, anaphylaxis cannot occur in a guinea pig from the repeated injection of guinea-pig serum, nor can the symptoms be produced in a horse by the injection of horse serum.

If we inject a guinea pig parenterally—that is, by any route except by the gastro-intestinal canal—it does not appear to suffer the slightest inconvenience. If, however, we inject this animal, two or more weeks later, with the same protein, it will die within one or two minutes and with very definite symptoms accompanying death. This is a manifestation of anaphylaxis.

For an explanation of this phenomenon we must go back to the work of Prof. Victor C. Vaughan upon the chemistry of the protein molecule. Vaughan has shown that a protein, treated chemically according to his method, is split into two parts—the one poisonous, the other non-poisonous. The *poisonous* part obtained from all proteins is the same whether it results from the splitting of egg white or from the splitting of typhoid bacilli; the symptoms leading to death in the guinea pig are identical. This poisonous part, then, is a poison and has no other function or effect; one dose has no bearing upon the effect of a subsequent dose, no hypersusceptibility is produced, and no tolerance, even by repeated administration.

The *non-poisonous* part, on the other hand, is specific in its action. The non-poisonous part of typhoid bacillus protein will immunize an animal against typhoid infection, but not against infection with colon bacilli; the non-poisonous part of horse serum will sensitize a guinea pig to horse serum, but not to goat or sheep serum.

These results of Vaughan's work upon the chemistry of proteins suggest an explanation of the mechanism of anaphylaxis; they show us that, instead of being the opposite of immunity, anaphylaxis is merely one of its manifestations; and, furthermore, they give us a clearer understanding of immunity itself.

When foreign proteins are injected into the tissues of an animal, the body cells at once set to work to remove this protein. They prepare a ferment capable of splitting the protein molecule, which possibly because of its size is not diffusible, into smaller fractions able to pass into the circulatory system and be thence eliminated. These fractions of the protein molecule are similar to those obtained by Vaughan in his chemical splitting; that is, a *poisonous* part which, after the first injection, is liberated slowly and is therefore harmless in its effect, and a *non-poisonous* specific part which stimulates the body cells to produce a specific ferment-like substance. About two weeks after injection the protein has been entirely removed from the tissues, the poisonous part has been eliminated so gradually that no symptoms have resulted, and the non-poisonous part has stimulated the tissues to generate a large amount of specific protein-splitting ferment.

At this point we must pause to note that, according to Vaughan, the protein-splitting ferment includes the antibodies so difficult to

understand in the theories of the German and French schools of immunity. This theory of the American school does not contradict the fact established by Metchnikoff, and further elucidated by Wright, that the white blood-corpuscles play an active part in the removal of foreign proteins, whether they be cells or fluids; nor is it out of harmony with the theory of Ehrlich, who gives to the group of antibodies—collectively called "the ferment" by Vaughan—different names according to their functions.

The guinea pig, then, at the end of two weeks after the first injection of, let us say, horse serum contains in his tissues no trace of horse serum; but he does have within his body a large quantity of protein-splitting ferment which may remain in the tissues for a long time; and, even if it disappears, the power to generate this ferment upon demand may remain permanently. If we now inject into this guinea pig a second dose of horse serum, the proteins contained therein are at once attacked by the specific ferment; digestion occurs almost immediately, resulting in the liberation of a large quantity of the poisonous part of the protein molecule; the animal is overwhelmed by it and dies usually in less than five minutes. A dose sufficiently large to cause death depends upon the method of injection; if injected into the circulation or into the brain, 1/20 c.c. is sufficient; if injected subcutaneously, however, at least 5 c.c. is usually necessary.

Now as to the bearing of this phenomenon upon infectious disease—Vaughan has used typhoid fever as a typical illustration. Infection results from the entrance of a few typhoid bacilli into the tissues under circumstances which permit their growth and multiplication. There is normally present in the body a small amount of a non-specific protein-splitting ferment which attacks the typhoid bacilli, liberating the non-poisonous part, which in turn begins to stimulate the tissues to the production of a specific anti-typhoid ferment. We know that in guinea pigs it takes from eight to fourteen days to produce enough ferment to cause serious symptoms of intoxication upon the injection of a second dose of the protein. Now this period corresponds exactly to the incubation period in typhoid fever. It is during this time that the typhoid protein-splitting ferment is produced in increasing quantities, while the typhoid bacilli are rapidly growing in numbers. The ferment sets free the poisonous part in gradually increasing quantities with the final appearance and progressive increase of fever and the other

symptoms of the disease. This process continues up to the point where the number of typhoid bacilli destroyed each day equals the number reproduced in the lesion. This balance is maintained for a time until the number of bacilli destroyed exceeds those reproduced.

A patient recovered from typhoid fever has remaining in his tissues a large amount of typhoid protein-splitting ferment, so that when typhoid bacilli again gain entrance to his tissues they are at once attacked and destroyed before they have a chance to develop. Obviously there is no intoxication, because the amount of typhoid proteins is infinitesimal compared to the amount necessary to result in anaphylactic shock.

It is now easy to understand the action of typhoid vaccine. When we inject beneath the skin a number of typhoid bacilli, their disintegration is started by the normal proteolytic ferments in the body. A second and third dose given at intervals of about ten days increases the quantity of specific typhoid protein-splitting ferment. The theory of typhoid immunity by means of bacterial vaccines applies equally to the production of immunity to other infecting bacteria. The theory underlying the use of bacterial vaccines in disease is based on the fact that the tissues affected are unable to produce a sufficient quantity of the specific ferment to overcome the infection. The injection of bacterial proteins in a healthy part of the body leads to the production there of these antibodies, which are conveyed to the focus of infection through the circulatory system and thus assist the local cells.

It will now be clear that the requisites to success in vaccine therapy are (1) that the vaccine injected must contain bacterial proteins identical in kind with those causing the infection, (2) that the ferment produced locally must come in contact with the infecting bacteria. For one with proper training it is not hard to determine the kind of bacteria causing an infection; nor is it hard to obtain either a stock vaccine representing these bacteria or to prepare an autogenous vaccine identical with them; and it is a very simple matter to inject these bacterial suspensions beneath the skin of the patient.

If the patient is not in the last stages of disease, there is not one chance in many thousands that his tissues will fail to produce the proper antibodies or ferments. If the patient shows no improvement as result of the treatment, it behooves the physician to use means by which the ferments may be induced to perform their function.

In some infections, as in staphylococcic infection, accessory measures are seldom needed, while in streptococcic infections they are nearly always necessary. In gonococcic infections of the urethra and prostate, the mere injection of vaccines accomplishes but little; in gonococcic infections of the joints, however, the vaccine is apparently sufficient.

We are indebted to Besredka of the Pasteur Institute in Paris for an improvement upon bacterial vaccines which constitutes a real advance in vaccine therapy. As said above, when the bacterial vaccine is injected beneath the skin a small quantity of the protein is split up by natural ferments and the specific non-poisonous part thus liberated stimulates the production of ferments which continue the disintegration until the maximum effect of the vaccine is obtained.

The ferment itself is composed of at least two constituents; one is specific, and by Ehrlich has been called *amboceptor* (the *opsonin* of Wright is a similar antibody). This substance has the power of fixing itself to the bacteria, thus preparing them for digestion by another substance which is not specific but is always present in the blood of healthy animals, and because the latter completes the ferment action it is called *complement.* Besredka proposed that amboceptor be utilized to prepare the bacteria for the immediate action of the complement. The amboceptor is obtained by injecting goats or sheep with massive doses of bacteria like those it is desired to sensitize. Bacteria thus prepared for the action of the complement were said to be "sensitized," and the suspensions of such bacteria were called by him "sensitized vaccines." The advantage they have over ordinary bacterial suspensions is that they eliminate the period during which the specific ferment is being formed. "Sensitized vaccines" have already been used extensively in France and also to a certain extent in England. The published reports amply attest their superiority.

Antibacterial Serums.

The so-called "therapeutic or antibacterial serums" include antistreptococcic, antipneumococcic, and antimeningococcic serums. These are prepared by the injection of horses first with dead and then with living bacteria. In the case of antimeningococcic serum injections of autolyzed bacteria are alternated with the cocci them-

selves. The autolysate contains a toxic substance which causes the production of some antitoxin. This serum, like antidysenteric serum, partakes, therefore, of the nature of both an antitoxic and an antibacterial serum.

These serums depend for their activity upon substances called ferments by Vaughan, but, according to the nomenclature of Ehrlich, "antibodies"; that is, substances antagonistic to the bacteria. Used in sufficiently large doses, antibacterial serums have undoubtedly great value. The chief difficulty lies in the fact that no method has so far been found by which antibacterial serums can be produced comparable in potency with diphtheria antitoxin.

It is well known that a much larger dose of any curative serum must be used if it is injected subcutaneously than if injected intravenously. Realizing this fact and the relative weakness of antibacterial serums, there is but little doubt that their use intravenously will be resorted to in the future with increasing frequency.

Summary.

1. There are two classes of bacteria with regard to their method of producing disease: (*a*) Those that produce soluble and diffusible toxins, and (*b*) those that do not.

2. The toxin-producing bacteria are the diphtheria bacillus and the tetanus bacillus.

3. Antitoxins produced by injecting horses with the specific toxins are antagonistic to the specific toxic products of the bacilli in a manner very similar to the antagonism between acid and alkali.

4. To the second class belong the great majority of the disease-producing bacteria.

5. The symptoms in the diseases caused by the latter are probably the result of the action of their specific metabolic products combined with the effect of the liberated poisonous part of their protein molecule.

6. Recovery from such infectious diseases depends upon the production of sufficient specific protein-splitting ferment to remove their causative bacteria from the tissues.

7. The amount of this specific protein-splitting ferment may be increased by injecting bacteria of the same kind beneath the healthy skin.

8. Immunity from infectious disease depends upon the existence

in the tissues of sufficient specific protein-splitting ferment to dissolve invading bacteria before they have a chance to develop.

9. The rational administration of bacterial vaccines presupposes accurate diagnosis and the administration of bacteria identical in kind with those causing the infection. It depends, furthermore, upon the ability of ferments and antibodies to come in contact with the infecting bacteria.

10. "Sensitized vaccines" are superior to ordinary vaccines because they reduce the preliminary period during which the injected bacteria are being split up so that the non-poisonous part may be available for the production of specific antibodies.

11. Antibacterial serums—antistreptococcic and antipneumococcic—depend for their activity upon their content in specific antibodies or ferments.

12. The amount of these ferments in even the best serums is relatively small, and the serums must therefore be used in larger doses than has been customary in the past.

13. Antimeningococcic serum is both antibacterial and antitoxic.

14. Since the efficiency of curative serums is increased many fold when administered intravenously, this route will be used more frequently than has been the custom in the past.

A CONSIDERATION OF AUTOGENOUS VACCINES.

By B. B. Vincent Lyon, A.B., M.D.

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Empiricism is dying. Throughout the last century, and particularly its latter decades, the searchlight of truth has lighted up many of the heretofore dark places in the study and practice of medicine. The discovery of the causation of many diseases through bacterial agencies was epoch-making, and led the way naturally toward the introduction of measures able to cope with such a foe.

During the last thirty years scores of men have been at work on this problem and have each added their little to the sum of our present knowledge, and from the time of Jenner one startling etiologic and therapeutic discovery has followed another, so that among the names destined to live will always be found those of

Pasteur, Koch, Pfeiffer, Ehrlich, Behring, Wassermann, Noguchi, and others.

Bacteria are divided into two classes, the good and the bad: saprophytic and pathogenic. The saprophytic bacteria are scavengers; they thrive best on dead tissues and assist in freeing the body of many waste products. Pathogenic bacteria thrive best on the living tissues of the host, in whom they are capable of producing disease. Their pathogenic action is due to the liberation of the toxins they contain or the elaboration of poisons in the tissues of the host.

Of these bacterial toxins there are two main types: The exotoxins, contained in bacteria whose poisonous principles are capable of being dissolved out of the bacterial cell. To this class belong the bacillus of diphtheria and the bacillus of tetanus. The great majority of bacteria, however, produce endotoxins, or poisons which are incapable of separation from the cell bodies by any of our known filtration methods. Examples of this are the bacillus of typhoid fever and the streptococcic and staphylococcic groups, etc.

While bacteria are capable of producing disease, it is not through their mere presence *per se,* for, as we know, our persons in health permit of the culturization of numerous pathogenic bacteria, therefore other factors must enter in, and these factors comprise the natural defensive mechanism of the body against disease.

Natural Resistance.—This varies greatly with the individual and has a certain selective action, for why is it that one person can harbor in his mouth virulent pneumococci and streptococci and yet can go through life without a single attack of pneumonia, and, conversely, be subject to repeated attacks of tonsillitis; whereas, another individual harboring the same organisms may have several attacks of pneumonia during his lifetime, and none of tonsillitis. This is due to the development of what we call *immunity,* which is the power of resistance the body tissues are able to exert against bacterial poisons. *Immunity* may be divided into species and racial immunity.

Species Immunity.—It is well known that many animals are naturally immune to diseases common to man, and that it is only with the greatest experimental difficulties that infections with those diseases can be made successfully.

Racial Immunity.—Also, among the different races of the same species there appears to be a natural immunity against certain

diseases, which have long been prevalent in that particular section, but which when carried to another section where fresh soil is obtained immediately light up into virulent epidemics. This is seen in the ravages of tuberculosis among the negroes and American Indians, and it is seen conversely in the immunity from yellow fever that has long been enjoyed by the negro.

Acquired immunity is the protection that is afforded an individual who has passed through an attack of one disease, this conferring a greater resistance to that disease in the future. This is commonly observed in diseases like typhoid and yellow fever. Acquired immunity may be either active or passive. "The process of conferring protection by treatment with either an attenuated form or a sublethal quantity of the infectious agent of a disease or its products is spoken of as active immunization," because the immunized individuals gain their power of resistance by taking an active physiological part in the acquisition of this new property of immunity. Thus active immunity can be acquired by repeated injections of attenuated cultures, as in Pasteur's work in hog cholera; by injections of sublethal doses of virulent bacteria, as demonstrated in the protozoön disease of Texas fever; by injections of killed bacteria, first suggested by Chauveau. This method of active immunization with gradually increasing doses of killed bacteria has been carried out successfully against many bacterial diseases. It is particularly useful against those groups of bacteria producing endotoxin; and, finally, by injections with bacterial products from poisons excreted or liberated from the bacterial cell body. These measures comprise *vaccination.*

Passive immunity, on the contrary, is that gained by the host through no active formation of antibodies on its own part, but rather accepting ready to hand the antibodies prepared by the tissues of another species. The most conspicuous types of this are the antidiphtheritic and antitetanic sera. These are both designed to meet bacterial exotoxins, and it is this type of sera that is most successful. On the contrary, antigonococcic, antistreptococcic sera, and the like, which depend for their activity on the lysin, opsonin, and other antibodies they contain, are not blessed with a like therapeutic success. Allen states that "these sera are not always curative; indeed, their use during active disease may not be altogether free from danger. Thus the administration of anticholera or antityphoid serum, which each depend for their activity on the lysin

they contain, may result in the extraleucocytic lysis of so many bacteria that the resultant flooding of the tissues with large quantities of their contained endotoxin may imperil the life of the recipient from the additional toxæmia."

Bacteria have a selective action: not only must they gain access to the body in large enough numbers and possessing sufficient virulence, but they must also gain entrance to a tissue that is suitable for their further development. For instance, you can rub a typhoid culture into an abraded surface of the arm or a culture of streptococci can be swallowed, both with equal impunity, but reversing the conditions a bacterial infection is sure to follow.

Now what are the general defences of the body against this bacterial invasion? They are fourfold:

1. *Antitoxin,* a substance manufactured by the tissues which is capable of neutralizing the soluble toxins produced by certain groups of bacteria.

2. *Agglutinin,* a substance which causes bacteria free in the tissues or blood stream to be clumped together in masses and held nearly immovable and therefore more accessible for phagocytosis. This is the more conspicuous where it concerns the motile bacteria. Though originally observed in 1889 by Charrin and Rogers, in studying the Bacillus pyocyaneus, the agglutination reaction is commonly associated with Widal, who first applied the phenomenon in the diagnosis of disease by an unknown organism.

3. *Lysin,* a substance or substances elaborated by the body which has the property of dissolving certain bacteria. Pfeiffer noted that guinea pigs which had been immunized against cholera bacilli could withstand the further intra-peritoneal injection of virulent cultures without harm, and found that the peritoneal fluids dissolved the organisms.

4. *Opsonin,* discovered and named by Wright, is a substance that prepares or sensitizes the bacteria for ingestion by the phagocytic elements of the white blood-corpuscles.

There are two types of bacterial infection: local and general. The former is best represented by boils; the latter is seen in diseases like typhoid fever, pneumonia, puerperal sepsis, and the like. When a person recovers from a bacterial disease like typhoid fever, it is by the body having gradually elaborated the foregoing antitoxins, agglutinins, lysins, and opsonins in amounts sufficient to cause the neutralization, destruction, and solution of the bacteria. The time

required in the manufacture of these substances varies in different diseases: 21 to 28 days, as a rule, in typhoid fever; 9 to 11 days, as a rule, in pneumonia, etc. So we have two biologic methods of treatment, serum and vaccine treatment, and the principle of the former is to supply these protective substances ready made (passive immunity) and in vaccination to stimulate the tissues to produce them more quickly, and, inasmuch as diseased tissues are more sluggish in locally manufacturing them, to utilize or exploit healthy tissues for the advantage of the enfeebled ones (active immunity). This, then, is the scientific basis for the action of vaccines. And now what are vaccines?

Vaccines are emulsions of the bodies of dead bacteria killed in various ways and suspended in suitable dosage in solution of normal saline.

There are two types of vaccines: heterogenous and autogenous. Heterogenous vaccines are prepared from infections similar to the case which is to be treated, but from infected material not derived from the patient himself. This type of vaccine may be, and usually is, polyvalent; that is, cultures are obtained from several infections of the same nature and therefore represent, possibly, several "strains" of the same organism. These heterogenous vaccines are commonly called "stock" vaccines, perhaps because they are prepared in quantities and held in readiness to be used in a given case on demand.

Autogenous vaccines are prepared from cultures grown from infected material obtained from the patient himself. In other words, they represent and are specifically the organism from the effects of which the patient is suffering and toward which you are assisting the patient to establish an immunity. Knowing these differences, it is not difficult to understand that biologists, bacteriologists, serologists, and clinicians of the thinking type are agreed that the autogenous group of vaccines fulfil best the scientific therapeutic requirements. Let me quote from an article recently published by a man whose authority is unquestioned: "With the exception of certain organisms, such as tubercle bacillus and the gonococcus, there is little reason for employing stock vaccines instead of autogenous, and there is abundant ground for believing that the use of stock vaccines will not only lead to carelessness of diagnosis and misinterpretation of the probable nature of the infection with consequent administration of the wrong species, but will sometimes be directly harmful.

"I am well aware that the argument has been advanced that laboratories are not sufficiently available to practitioners in all sections to make it possible for them to obtain autogenous vaccines, and would reply that in a measure this may sometimes be true; but the general demand for stock vaccines has been artificially stimulated by manufacturers, and the practical application of this method of treatment has outdistanced the scientific investigation of its merits. Instead of wholesome growth with the gradual provisions of local agencies where autogenous vaccines could be obtained, an unwholesome growth of this mode of treatment has been stimulated, and those who seek to keep up with the latest pronouncement of advertisement literature find themselves in a position of dependence upon stock vaccines in many cases. There can be no doubt that in some instances stock vaccines are satisfactory. Staphylococcus and typhoid and tuberculosis vaccine are instances, but the other forms, and especially streptococcus and pneumococcus and mixed vaccines, are of very doubtful efficacy.

"Here we come upon the field of variability in the organisms themselves, and, unless a growth has been prepared from the patient himself, the strain may be entirely different and inappropriate. It avails little to use mixed strains which require the reduction of dosage of the one possibly present and available strain below the point of usefulness because of the simultaneous injection of several other strains in the mixture which are of no use, or practically useless.

"As for stock mixture of heterogenous organisms designed for the treatment of cases in which no sort of accurate bacteriological diagnosis has been made, too vigorous condemnation cannot be phrased."

In my own personal experience I have met with many cases referred to me by other practitioners, cases on whom various stock vaccines had been tried for various lengths of time, in various dosages, with absolutely no improvement, and which have responded with surprising promptness to an autogenous vaccine, and have established an immunity that in many cases has lasted for years, and I personally have used in some cases stock vaccines of different types, giving them a thorough trial, only to become discouraged at their non-success, and have discarded them in given cases for autogenous vaccines with gratifying results.

On the other hand, I believe that stock vaccines of a single

or of a polyvalent single organism type have their place, and a very important place of usefulness, in the 48–96 hour interval that is often necessary to prepare the autogenous vaccine, after the bacterial identification in the specific case has been established, and I almost uniformly use this period to give one and sometimes two injections of the appropriate stock culture. Appropriate stock cultures may often be used with value in association with autogenous vaccines in selected cases.

A word or two now to ensure success in getting the proper bacterial results in culture taking. The first principle is to obtain your material free from contamination, and this requires the observance of special precautions according to the kind of material that is to be cultured.

Urine: Should always be obtained by sterile catheter, after the external meatus has been appropriately cleansed, and drawn off into a sterilized flask or bottle, to which no preservative should be added. It is better to catheterize the day specimen into one receptacle and the night urine into a separate one.

Feces: Should be obtained, urine-free, and specimens from first and last portion of the stool obtained and studied.

Sputum: Should be obtained with greatest care, because for practical purposes no mouth is germ-free, and alveolar pyorrhœa, infected tonsils, and the like are so common. Before retiring, the mouth should be carefully rinsed with sterile water and the teeth brushed with sterile toothbrush, and a closed vessel containing sterile water placed at the bedside. In the morning the mouth should again be rinsed thoroughly with the sterile water, gargled, and with the brush re-sterilized, by dipping in boiling water, the teeth should be thoroughly brushed and then a few mouthfuls of clean sterile water should be swallowed. After this the sputum should be expelled by coughing and caught in serial sterilized wide-mouth bottles (with sterile corks), and it is best that only one or two masses of sputum should be expelled into any one bottle and the bottles labelled and sent at once to the bacteriologist for immediate examination. The sputum should, after direct examination of stained specimens to determine morphologically the different types that may be present, be then "whipped" through several Petri dishes containing sterile water to further free the bacteria from surface contamination, and the final washed specimen planted upon the different culture media that will appear best suited for

their recovery in pure culture, as judged from the findings on the first direct examination.

Cultures taken from *boils,* or from *infected sinuses,* from *acne pustules,* from *tonsillar follicles,* and the like, should be made only after thorough appropriate cleansing and disinfection of surface relations, and then taken from a second or third portion of the material, discarding the first, by means of a platinum wire or a sterile capillary glass pipette inserted well within the cavity.

Cultures from *eye, ear,* or *nose* should have appropriate measures to secure success.

Blood specimens should always be obtained from a vein, preferably at the bend of the elbow, by means of an all-glass sterilized syringe of a capacity not less than 5 c.c. It is rarely necessary to cut down on a vein, but the arm should be thoroughly sterilized by tincture of green soap and water, by 5–10 per cent. lysol, by absolute alcohol, and finally by ether; personally I prefer not to use iodine. It is better to moderately tourniquet the upper arm before sterilizing the field in order to prevent thin-walled veins from collapsing under the pressure. The blood should be immediately plated and flasked in peptone and dextrosed broth.

In Pulmonary Abscesses: In suitable cases material may be obtained by lung puncture in the following way: After sterilizing the chest wall in the same manner as for blood cultures, the needle attached to an all-glass syringe, containing 3 c.c. of peptone broth, should be plunged into the lung at the proper point, as determined beforehand by clinical means, and 1 c.c. of the broth introduced and then reaspirated as far as possible and tubed. This measure will yield results in many cases properly selected clinically.

After getting suspected infected material, direct examination by means of variously-stained slide specimens should be made to determine morphologically and by staining reactions and relations whether one or more types of organisms are present, and, if the latter, how many and what types, and then, aided by this knowledge, proceed to utilize the various culture media that will best ensure recovery of each organism in pure culture. Here is where the thoroughly-trained bacteriologist will succeed and in the shortest time. It is often exceedingly difficult to recover a shyly-growing streptococcus or tubercle bacillus occurring in small numbers, let us say from a urine practically alive with the *Bacillus coli.* This may be accomplished by inhibiting or attenuating the growth of the

hardier, more freely growing organism by treating the culture medium in an appropriate manner, but unless this is accomplished it will be seen at once how useless it is to successfully treat a pyelitis of streptococcal or tubercular origin by using only the *B. coli* in the vaccine preparation. Hence the failure of many autogenous vaccines that are bacteriologically imperfect or incomplete.

In many cases of *chronic gleet,* however, the gonococcus is absent and the catarrhal inflammation kept alive by secondary invaders, which may then in combination serve for cure in absence of the primary invader.

After getting out every bacterial group contained in a given specimen, each in pure culture, these should then be studied with a view to their share in the production or continuation of the disease in question, and, guided by experience, clinical as well as bacteriological, a final judgment of the organisms concerned may be passed and the proper ones selected for use in the vaccine. They may all be combined in a single ampoule or may be placed singly or in pairs. Only the lower dosages, however, can be reached by making a mixed vaccine composed of many elements, on account of the combined dosage being too high to permit of safe injection.

We can now proceed to prepare the vaccine, in which the following steps are concerned:

1. To obtain an emulsion containing the bacteria in purity—an emulsion with a uniform suspension and as free from bacterial clumping as possible.

2. To standardize the emulsion—that is, to determine how many bacteria are contained in each cubic centimetre.

3. To kill the bacteria in the emulsion and then tube them—or

4. To decide upon the dosage of each ampoule or set of ampoules; to tube them still alive and then kill them.

5. To label, effectively, each ampoule and place them in sets of ten in compartment boxes or cartons, the lids of which are to be specifically marked with the names of the organisms they contain and in what dosage, and most particularly with directions for their use.

6. To be sure that all "controls" are sterile before allowing the vaccine set to leave the laboratory for use.

I shall not in this paper enter in detail into the technic required in the actual preparation of the vaccine, but I want to say a word

or two of caution to most carefully consider the best ways of killing the bacteria without impairing their immunizing properties. This can only be accomplished by a thorough knowledge of and observance of the thermal and chemical death-point of each group of organisms: a knowledge that will tell you which bacteria should be killed by heat and which by chemical measures, or by a combination of the two. If by heat, at what temperature and for how long sustained? If by chemical sterilization, by what chemical and in what strength? I have known many an autogenous vaccine—otherwise quite appropriately selected bacteriologically and otherwise faultlessly prepared—to be inert and to fail absolutely therapeutically for no other reason than that the thermal and chemical death-points were not carefully ascertained. And I doubt not that this applies equally to many stock vaccines.

Have we in vaccine therapy a means sufficient to combat all types of bacterial infections? I would answer emphatically "no," and I would add that harm may often come from their indiscriminate use and in the hands of the inexperienced and careless.

In epidemic meningitis, in typhoid fever, in pneumonia, in generalized bacteræmia, with or without ulcerative endocardial lesions, the use of vaccines for curative purposes has not been attended with great success, although occasionally a case is seen in which amelioration in severity of symptoms has taken place which rightly or wrongly has been ascribed to the use of the vaccine. I am by no means yet convinced that their use in such cases is unjustifiable, and believe that we may yet arrive by experience at some method of establishing proper dosages and proper intervals of injection for this class of acute fulminating infections that will produce better results.

The most suitable field for vaccines and the field in which the most brilliant results have been obtained lies in treatment of diseases, acute or chronic, that have a local focus of infection, such as furunculosis, carbuncles, abscesses, various bone infections, such as osteomyelitis, various skin infections, such as acne vulgaris, infected sinuses, pyelitis, empyema, various infections of the mouth, such as pyorrhœa alveolaris, infections of the nose and nasal passages and various post-gonorrhœal conditions, and various conditions of the respiratory tract.

And now a final word as to why vaccines fail in the hands of many workers, even in the above field of election—chiefly because

of insufficient knowledge governing the general laws of dosage and time intervals of injection; by selecting inappropriate points of injection; by disregarding the best time of day at which injection should be given, so that the patient isn't safeguarded during the "negative phase" period at which his antibody formation is at the lowest ebb, etc. For many of these points I would refer the student or interested worker to a close perusal of monographs on this subject, notably Allen on "Vaccine Therapy."

Finally, I would call attention to a common cause of failure in a neglect to realize that autogenous vaccines need to be frequently freshly renewed—*i.e.*, a new culture taken and a new vaccine prepared from cultures that represent more nearly the *status præsens* of the case; for it frequently happens that in long chronic conditions the bacteria, by mutation or other biological properties, become adapted more or less to the antibodies formed in the tissues of the host.

I was asked, before reading this paper before this body, whether I did not think it quite feasible and quite proper for druggists to establish autogenous and stock vaccine departments for the purpose of themselves making these products. I think I must already have answered this question to most of you. I do not think it is practical nor fitting that you should, nor do I believe that it would prove commercially a success. And let me close with the words of Sir Almroth Wright, one of the pioneers in this work, who states that for such skilled service as that demanded for vaccine therapy "is required a man who has spent years of study to master the technic; to know how to make the vaccines, to know where to look for the microbes, to know how to isolate them, and, most of all, a man with sufficient experience and ability to apply all these things."

1901 Pine Street, Philadelphia, Pa.

THE CHEMISTRY OF A CUP OF COFFEE.

From time to time numerous analyses of coffee have been made and published which, while giving some insight into the chemistry of the coffee berry, have not necessarily enlightened us as to the position of affairs in regard to the liquor obtained when coffee is prepared in the way commonly enjoined. The chemistry of the cup of coffee will obviously leave out of consideration the chemistry of

the "grounds." It is the infusion with which the following laboratory notes deal, and certain fresh indications, we believe, have been obtained which are worth presenting in view of their medical interest. The story is far from complete, but there are interesting incidents in it which, as far as it goes, are worth recording.

A Comparison between Coffee and Tea.

From a pharmacological or, what should amount to the same, a dietetic standpoint tea or coffee ought in certain ways, at all events, to act similarly, since both contain the alkaloid caffeine which has a well-known and marked effect of stimulation upon the central nervous system. It is generally admitted, however, that the two beverages, though having one thing in common, afford different results. Tea, it is well to point out, contains a much larger proportion of the alkaloid than coffee, but in the preparation of tea in ordinary domestic practice a much smaller quantity of material is used than is the case with coffee. A common formula enjoined in the making of tea amounts to the preparation of 1.25 per cent. infusion of the leaf. Similarly, in the preparation of coffee the quantity of coffee usually directed to be used signifies a 6 per cent. decoction. Since tea contains from 3 to 4 per cent. of caffeine, and coffee seldom more than 1 per cent., it follows that as regards this alkaloid both infusions of coffee and tea made on common domestic lines will contain practically the same amount of caffeine volume for volume of fluid. The inference is that whether it be a cup of coffee or of tea, the dose of alkaloid will be the same. But according to the present investigation the caffeine in coffee infusion has quite different associates from those in tea. This would appear to be the case, inasmuch as while little caffeine is extracted from tea by cold water, we find that practically the whole of the caffeine in coffee is taken out. There seems to be little doubt, as we have shown in previous articles upon tea,[1] that the caffeine in tea is for the most part combined with tannin in the form of caffeine tannate, which is not very soluble in cold water, but is easily soluble in hot water. We think this is an important observation, for it points to the probability of caffeine existing in coffee in a quite different form which is

[1] "The Chemistry, Physiology, and Æsthetics of a Cup of Tea," *The Lancet*, Jan. 7th, 1911, and Dec. 2nd, 1911.

easily soluble in cold water. Subsequent experiments showed that the caffeine in coffee is combined with a peculiar acid allied possibly to tannic acid, but exhibiting different properties from the tannin present in tea. Thus this acid (it has been called caffetannic acid by some observers) is not particularly astringent, has a sour coffee-like taste, does not coagulate gelatin, gives a light green colouration with perchloride of iron (whereas tannic acid of tea turns it black), does not make caffeine solutions thick as does tannic acid, does not precipitate alkaloids—*e.g.*, quinine—and, in fact, shows altogether different properties from the tannic acid of tea. It gives a precipitate, however, with lead acetate from which the acid can be separated by sulphuretted hydrogen. When coffee infusion is saturated with ammonium sulphate a precipitate is obtained which contains a small proportion of the total caffeine in the free state, whereas a tea infusion similarly treated gives an abundant precipitate containing nearly all of the caffeine, this precipitate according to our observations consisting chiefly of caffeine tannate.

The Absorption of Caffeine Modified by its Associates.

The caffeine tannate of tea is precipitated by weak acids, and the presumption is that it is precipitated by the gastric juice, and therefore the caffeine is probably not absorbed until it reaches the alkaline alimentary tract. In the case of coffee, however, in whatever form the caffeine may be present, it is soluble in both alkaline and acid fluids, and therefore the absorption of the alkaloid probably takes place in the stomach. This fact may have an important physiological significance when we consider the comparative stimulating effects of the two beverages. If our view is correct coffee should act more promptly than tea as a stimulant and restorative, looking to its physiological action as due for the most part to caffeine. In practice it is generally accepted that coffee is a more powerful restorative than tea. The use of strong coffee as an antidote in poisoning by narcotics, notably morphia, is of interest in this connexion. Tea is mentioned for the same purpose, but only rarely. Apart from the consideration that caffeine has probably a more rapid action when taken in the form of coffee than in the form of tea, because the caffeine in coffee is more readily absorbed, it must also be remembered that coffee is often made with a generous proportion of the powdered bean, as in the case of the after-dinner "black" coffee,

the view being that the secret of good coffee is to make it strong. This, of course, is an entirely æsthetic demand, which may likely enough be opposed to physiological morality.

The Strength of Cold Water Extracts of Coffee Compared with Boiling Water Extracts.

The fact that the caffeine in coffee is completely soluble in cold water suggested making a comparison as to the composition of the cold and hot water infusions in regard to other constituents. For this purpose several types of coffee were chosen, all of which reached this country through Costa Rica. As will be seen from the accompanying table, the varieties examined were as follows: Raw (*i.e.*, unroasted) Costa Rica, common quality; raw Costa Rica, finest quality; pale roasted Costa Rica, common quality; pale roasted Costa Rica, finest quality; high roasted Costa Rica, common quality; and high roasted Costa Rica, finest quality. The results are instructive, and we may proceed to consider the differences in composition of the infusions, both cold and hot, shown where raw, pale roasted, and high roasted coffee are employed, and the relationships, if any, of these differences to the discrimination supplied by the expert taster, who describes a particular coffee as, in his own words, "common" or "finest."

It is a somewhat remarkable fact that cold water extracts from coffee the same weight of materials as boiling water, but it must be admitted that the former infusion is somewhat less palatable than the latter. Chemically, however, there is little difference between them, and we may presume that physiologically a cold water extract of coffee will be much the same as a hot water infusion, leaving out æsthetic considerations, although these, of course, are exceedingly important, from all dietetic aspects. It is probable that cold water fails to extract certain oily bodies or fats which contribute attractive taste and aroma. The total extract is frequently higher in cold than in hot water. And not only is caffeine extracted from coffee equally well by cold and hot water, but this is true of the mineral salts and of the peculiar acid known as caffetannic acid, the acid which corresponds to the tannin of tea. In regard to the proportion of materials soluble in cold water coffee shows an entirely different result to tea, inasmuch as while coffee yields about 25 per cent. of its weight to cold water (an amount which is not increased

when hot water is used) tea yields only 12 per cent. of its weight to cold water, which is increased to 25 per cent. when the infusion is made with hot water. Again, cold water extracts from tea only 17.5 per cent. of its total caffeine, while from coffee it extracts the whole. Similarly, cold water extracts from tea 13 per cent. of its total tannin, while coffee under the same treatment yields practically the whole of its caffetannic acid.

The Effect of Roasting.

An infusion of green or unroasted coffee is singularly nasty to the palate, and it follows that the roasting process renders coffee the palatable article that it is. The chemistry of roasting amounts largely to a caramelisation process, during which certain oils and aromatic principles are formed as products of a mild destructive distillation. Curiously enough, there is little loss of caffeine in this process, as our results show, which is remarkable in view of the fact that caffeine sublimes at high temperatures. There are two degrees of roasting adopted—viz., pale roasting and high roasting. The important chemical effect of roasting, according to our analyses, is to diminish considerably the amount of caffetannic acid. If the figures in the table be consulted it will be seen that while in an

The Analysis of Hot and Cold Infusions of Coffee.

Constituent.	Raw Costa Rica (common).		Raw Costa Rica (finest).		Pale roasted Costa Rica (common).	
	Hot infusion.	Cold infusion.	Hot infusion.	Cold infusion.	Hot infusion.	Cold infusion.
Total extract.....	29.16	30.83	29.60	31.50	25.33	24.00
Ash of extract.....	4.16	3.88	4.00	3.88	4.16	5.66
Caffetannic acid.....	9.60	8.63	9.66	7.83	6.10	5.80
Total caffeine	1.00	1.33	1.21	1.56	1.11	1.11

Constituent.	Pale roasted Costa Rica (finest).		High roasted Costa Rica (common).		High roasted Costa Rica (finest).	
	Hot infusion	Cold infusion.	Hot infusion.	Cold infusion.	Hot infusion	Cold infusion.
Total extract.....	23.50	25.66	24.30	24.00	25.60	23.00
Ash of extract.....	3.50	4.50	4.66	4.00	4.00	4.50
Caffetannic acid.....	6.60	5.90	3.90	3.16	3.63	3.87
Total caffeine	1.05	1.06	1.23	1.11	1.05	1.20

infusion of raw coffee (unroasted) the caffetannic acid amounts to 9.60 per cent., it is in the pale roasted 6.60 per cent., while by further roasting, as in the "high roasted," it is reduced in the infusion from 3.63 to 3.90 per cent. What part caffetannic acid exactly plays as a dietetic constituent of coffee it is difficult to say, but if it should prove to be an undesirable element, then the high roasted coffees are least open to objection on this account. It may be noticed also that the raw coffee yields a greater percentage of soluble constituents to both cold and hot water than high roasted coffee, the pale roasted coffee showing intermediate results. Roasting, amongst other things, has, therefore, the effect probably of rendering certain bodies insoluble—*e.g.*, albumins—while the slight burning effect upon carbohydrates would produce possibly some free and of course insoluble carbon.

Quality of Coffee in Relation to Chemical Composition.

From the results recorded in the table it will be seen that no definite relation can be traced between the æsthetic quality of coffees, classed respectively as "common" and "finest," and the chemical composition of the infusions which they yield. It may be noted that there is no important difference in the amount of the drug caffeine when the common and finest varieties are examined. It is probable that the æsthetic values—flavour, body, aroma, and so forth—are related in some way to the amounts of oil bases or aromatic principles present, and these are in any case minute. Whether they are present in appreciable quantity or not doubtless depends upon the care spent upon the roasting process. At any rate, it is conceivable that a point in the roasting process could be reached which would deprive the coffee of all attractive flavour, while it is certain that the infusion of the raw unroasted berry is not fit to drink on account of its unpleasant taste. Recently it has been announced on more than one occasion that pyridin is an important constituent of coffee. We have certainly found it present, but not in sufficient quantities to estimate. It is rather a curious fact that some authorities mention that coffee often relieves asthma, while pyridin is described as "useful in the treatment of asthma" and "beneficial in cardiac dyspnœa, emphysema, and angina pectoris," and, finally, that "it is probably the relieving agent of various cigarettes and powders smoked or burnt for asthma and whooping-cough." Another constituent of coffee

produced by roasting is caffeol, a nitrogen-containing oil, but it would be impossible to differentiate the quality of coffee upon an analysis pursued in this direction, inasmuch as the amount found does not exceed more than 0.06 per cent. It is doubtful whether it has any further value from a dietetic point of view than that supplied by its influence in pleasing the senses. When isolating caffeine from coffee infusion the solvent (chloroform) takes out also a non-crystalline substance which unlike caffeine is soluble in ether. This substance has a very strong, pleasant, but somewhat bitter flavour of coffee. The yield is different according to the quality of the coffee examined, and it is possible that this principle is a determining factor in the judgment given by the expert coffee taster. It is a product of roasting and does not exist in raw coffee.

Food Value of Coffee.

The infusion of coffee presents practically very little material that is of direct nourishing value, but by diminishing nervous fatigue, by virtue chiefly of the caffeine present, it may increase muscular power. It is not itself a builder of tissue. The use of coffee after dinner, it is of interest to note, is justified in a large number of cases by the fact of its stimulating effect upon the vital centres, and it is said to serve to some extent as an antidote to alcohol. It is commonly claimed to remove drowsiness; as a matter of fact, in many subjects it produces drowsiness, but this is usually followed quickly by marked wakefulness. The practice of drinking coffee after a meal for the sake of the stimulus which is experienced has much to be said in its favour dietetically. There is no reason for supposing that coffee possesses any value as a food. The berry contains a quite important proportion of fatty substances (12 per cent. average), but these are necessarily excluded from the infusion, as owing to their insolubility they remain in the "grounds."

According to our analyses again the protein contents of a cup of coffee are small, approximating to 1.25 per cent. of the coffee extracted. This amount can have little dietetic significance. There is also a trifling quantity of dextrin and sugar present besides traces of alcohol, which again can possess no importance from a physiological point of view.—*The Lancet,* Nov. 29, 1913, pp. 1563–1565.

BOOK REVIEWS.

PHARMACEUTICAL BOTANY. By Heber W. Youngken, Assistant Professor of Botany and Pharmacognosy at the Medico-Chirurgical College, Philadelphia. P. Blakiston's Son & Co., Philadelphia.

To speak of this little book of less than a hundred pages as a dictionary or a glossary is not to belittle its value to the student. The illustrations, as, for example, those on stem and leaf structure, are especially well chosen, and their pictorial value is worth many words of text, which, of course, is not a factor of this book. From almost any aspect of thought the book seems like a list of terms, but these terms are well arranged and with a good regard to system. The desire to make the definitions brief has made them in many cases almost meaningless except just as a reminder to one who already knows what the term means.

As a whole, the acknowledged desire of the author has been well attained, but there is a question whether such an object is especially advisable. A student is apt to be just as human as the average person with a consequent eagerness to have before him a volume which is " readable " even though it is for purposes of study. The feeling arises in us, as we look over the volume in hand, that it is a mighty nice little book to turn to once in a while, but that it would rather strain our devotion to science if we were called upon to use it as a text-book from which to gain our first insight into a new subject.

A. K. LOBECK.

ANNUAL REPRINT OF THE REPORTS OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION for 1913, with the Comments that have appeared in the JOURNAL.

" The more strictly scientific parts of the reports, both from lack of space and because of their technical nature, have been abstracted or entirely omitted from the reports as published in the JOURNAL. Believing that these scientific investigations should be available to scientists in general, especially to chemists, pharmacologists, and others interested in medicine, the Council has authorized the preparation of this volume, containing the complete reports of the Council adopted prior to January 1, 1914, as well as the comments which have appeared at the time of publication."

These reports are a valuable addition to the literature that has

accumulated in the last few years on proprietary remedies and nostrums.

Previous to the last decade investigative work of this sort in reference to remedies of this kind was hardly thought of, although there may have been dreamers who had hopes and visions of what the future might bring forth. We do not use the word "dreamers" in any offensive sense. Dreamers with initiative and honesty of purpose are the compelling force in this world, and it is gratifying to know that there are men of this type in medicine and pharmacy who are willing to work disinterestedly for the body politic.

Pharmacists who desire to add to their efficiency and usefulness would do well to add these reports, which have been appearing for several years, to their libary.

JOHN K. THUM.

NEW AND NONOFFICIAL REMEDIES, 1914: Containing Descriptions of the articles which have been Accepted by the Council on Pharmacy and Chemistry of the American Medical Association Prior to January 1, 1914.

This work epitomizes one phase of the revolution that has taken place in medicine the last decade. It typifies the passing from darkness into the light of reason of things pharmacological, or rather the exploitation of modern materia medica. Indeed, it fills a long-felt want in both the profession of medicine and pharmacy. When one stops to consider the inaccessibility of information relating to unofficial remedies previous to its publication it hardly seems possible that we ever got along without it.

Essential information relating to biological remedies such as serums, vaccines, and tuberculin preparations is given in a manner convenient to the seeker after such knowledge.

JOHN K. THUM.

CURRENT LITERATURE.

UNIFORMITY IN DRUG STANDARDS.—In a contribution to the *Journal of the Kansas State Medical Society*, entitled "A Plea for Uniformity in Drug Standards and for Uniform Requirements in Dispensing," L. E. Sayre makes some interesting observations. "If what is prohibited within a state is permitted beyond its borders,

the statutes of prohibition become not only inefficient, but most useless. If what is prohibited within a drug store is permitted in a physician's dispensary, the law likewise becomes measurably inoperative as far as the public is concerned."

He makes the statement that such conditions exist and that in some of the different states the evil has been exposed. He quotes Mr. Roemer, who, at a meeting of the New York Pharmaceutical Association, made the announcement that an investigation of some of the medicines dispensed by physicians showed a sad state of affairs; heroin tablets containing no heroin, morphine tablets without morphine, and elixir of terpin hydrate in which the terpin hydrate was conspicuous by its absence!

Mr. Sayre believes that the interest of the public could be safeguarded by the state laws requiring all medicine dispensed by physicians to *bona fide* patients to conform to legal standards, and, further, that any place where drugs are compounded, dispensed, or sold should be amenable to official inspection.

If dispensing by medical men has resulted in conditions which are prejudicial to the public health—and from this standpoint alone should the question be viewed—then legislative regulation must, and no doubt will, be undertaken by the various states. This question is beginning to loom up as never before and must be settled sooner or later. It probably would be a good plan if the various state medical and pharmaceutical societies at their coming meetings for the year were to take hold and thresh this matter thoroughly and formulate some definite opinion upon the whole subject.

JOHN K. THUM.

CHEMICAL EXAMINATION OF DICOMA ANOMALA. By Frank Tutin and William J. S. Naunton. The Wellcome Chemical Research Laboratories, London.

The material employed for this investigation consisted of the entire air-dried plant of *Dicoma anomala,* Sond., obtained from South Africa.

An alcoholic extract of the plant, distilled in a current of steam, yielded a small amount of an essential oil. The portion of the extract which was soluble in water yielded a small amount of a colorless crystalline glucoside, and a large amount of a yellow amorphous product, which, on hydrolysis with alkali, gave 3:4-dihydroxycin-

namic acid. The aqueous liquid contained, furthermore, a quantity of sugar which yielded d-phenylglucosazone, melting at 218°.

The portion of the extract, which was insoluble in water, formed a dark-colored, resinous mass. It consisted largely of amorphous products, some of which gave 3:4-dihydroxycinnamic acid on hydrolysis, and a small amount of an amorphous alkaloid was also present. The following definite substances were obtained from the resin: Hentriacontane $C_{31}H_{64}$; a phytosterol $C_{28}H_{46}O$; palmitic, stearic, arachidic, cerotic, and melissic acids, together with some unsaturated acids which appeared to consist chiefly of a compound, $C_{16}H_{30}O_2$, such as has been obtained by Bull (*Ber.*, 1906, 39, 3537) from cod-liver oil.

J. K. T.

PHILADELPHIA COLLEGE OF PHARMACY.

Annual Meeting.

The annual meeting of the Philadelphia College of Pharmacy was held March 30th, at 4 P.M., in the Library; the President, Howard B. French, presiding. Twenty-two members were present. The minutes of the quarterly meeting held December 29th, 1913, were read and approved. The minutes of the Board of Trustees for December 2nd, 1913, January 6th, February 3rd and 9th were read by the Registrar, J. S. Beetem, and approved.

President French delivered his Annual Address, when Mr. Beringer moved that the address be referred to the Publication Committee, as there were many items of information that should be given to the public through The American Journal of Pharmacy, particularly the items referring to the instruction as given in the College. Seconded, and so ordered. (See p. 233 in this issue of this Journal.)

Report of the Publication Committee was read by Professor S. P. Sadtler. The Journal has been published regularly during the past twelve months. The financial statement presented shows a creditable balance after paying all bills. It is impossible to supply a complete set, as some of the earlier volumes have one or more numbers missing. It is hoped that the sale of back numbers will increase so that a general index since 1890 can be published. There is need for such an index, as is shown by a number of inquiries for

one, and even orders have been received. In discussing the report Mr. Beringer asked if it was possible to reprint the missing back numbers in order to supply complete sets. Professor Remington suggested making use of a photographic process, in place of printing, to replace back numbers, when Mr. England moved that in order to secure reprints of back numbers the subject be referred to the Publication Committee, with power to act. So ordered.

REPORT OF COMMITTEE ON PHARMACEUTICAL MEETINGS.—Professor Kraemer said that the work done during the past few years has not been all it should be, owing to the fact that (as there are so many pharmaceutical societies in Philadelphia) there was a corresponding division of energy. Yet there are some indications that our College may be able to come back to the work in the old spirit and with renewed vigor. In addition to the meeting last May, when the students of the graduating class presented abstracts of their theses, there have been three other meetings held. The first of these was in October, when Professor Eugene Charabot, of Paris, gave a charming address in French on "The Formation and Distribution of Odorous Products in Plants." This was rather a unique occasion in that a large number of students were present and nearly every one expressed delight in the privilege of hearing this discourse. The article was printed in full in the JOURNAL, translation having been made. He also stated that he had just received a request from the editor of a Hungarian periodical to reprint the address.

Another meeting was held in November. Professor La Wall had an article on the "Detection of Chicory in Decoctions of Chicory and Coffee." This paper caused a great deal of interest, and was published in full in the JOURNAL. Mr. Boring exhibited several specimens of elixir of iron, quinine, and strychnine, and Professor Remington gave an illustrated lecture on "Some Pharmaceutical Celebrities I Have Met"; also touching on the pharmaceutical colleges and the professional aspect of pharmacy in Europe, especially England and Germany.

The third meeting was held in February, when Mr. Lobeck gave a talk on "A Roughing Trip Across the Continent," illustrated with colored photographs. It was a very practical talk not only on how one should arrange a vacation, but to get the most out of it.

EDITOR'S REPORT, read by Professor Kraemer. During the past year we have published 572 pages, exclusive of a 10-page index. This matter included 75 original and selected papers covering a wide

range of subjects relating to pharmacy. We have received the support of investigators in various parts of the United States and those connected with other colleges; our own members continue to contribute articles and in other ways promote the objects of the JOURNAL. The following graduates have contributed articles during the year: George M. Beringer, George M. Beringer, Jr., Dr. Robert A. Hatcher, Victor O. Homerberg, Henry Kraemer, Professor Charles H. La Wall, Dr. Frederick B. Power, Sister Bertha Müller, Professor Joseph P. Remington, John R. Rippetoe, John K. Thum and M. I. Wilbert, and from the Honorary Members: Professor Charles E. Bessey, Professor W. G. Farlow, Professor A. Tschirch and Dr. A. L. Winton.

The Quarterly Report on Progress in Pharmacy, by M. I. Wilbert, continues to be one of the important features of the JOURNAL, as it gives an excellent *résumé* of discoveries of interest to medicine and important happenings in pharmacy. During the past year we have published a number of general articles which have given in a nutshell some of the advances in modern science. Among these articles we mention Ehrlich's Chemical Therapy, Phylacogens, Colloids and Crystals, Enzymes, and Phenomenon of Catalysis.

CURATOR'S REPORT, read by J. W. England. The Museum of the College is growing yearly in importance. The entire collection of drugs and drug products and the Martindale Herbarium should be relabelled. The containers for the drugs should be standardized to two sizes only. The Museum could be made more valuable to the pharmaceutical public as a place of reference for standard or typical drugs and drug products, and most interesting also to the general public, if the historical collections were properly displayed. The Museum consists in large part of typical specimens of rare drugs. It should be improved by the addition of typical specimens of the more commonly used drugs as well, and especially by a proper display of our historical matter and apparatus.

The recommendations and suggestions in the Curator's report were, on motion, referred to the Board of Trustees.

LIBRARIAN'S REPORT, read by Professor Sadtler. During the year the Library has added by purchase, gifts, and exchanges a total of 105 volumes, 80 volumes of periodicals and theses have been bound, 2384 books have been accessioned, classified, and shelf-listed, making a total of 7264 books ready to be catalogued. Use

of Library during the year by 1375 persons, an increase of 378 over last year.

The report of the Committee on Nominations was read and ordered, entered and filed.

A communication was read from C. Carroll Meyer, declining the nomination for membership in the Board of Trustees because of pressure of business preventing his attendance at the meetings.

The President appointed Professor F. X. Moerk, Mitchell Bernstein and E. H. Hessler tellers, to conduct the election. The report of the Committee on Nominations being again read, the members proceeded to a ballot. While the ballots were being counted, Professor Stroup alluded to a recent notice received from the Fire Marshal and quoting an Act of Assembly prohibiting smoking in any part of the building. He hoped there would be some modification of the rule so as to permit smoking in the corridor, which was entirely fireproof. Past experience had shown that when prohibition was enforced the entrance and the street in front of the College were used as a place for smoking and a number of complaints and police troubles had resulted. A number of the members related various experiences, viz., President French, Professors Remington, Kraemer, Sadtler, Lowe, Messrs. Beringer and Poley; the speakers generally thinking that, while protection from the risks of fire was absolutely necessary, some means should be devised to permit smoking in some part of the building. The discussion was closed by President French stating he would confer with Director Porter regarding the matter.

The tellers reported the results of the election as follows:

President, Howard B. French; first vice-president, R. V. Mattison, M.D.; second vice-president, J. L. Lemberger; treasurer, Richard M. Shoemaker; corresponding secretary, A. W. Miller, M.D.; recording secretary, C. A. Weidemann, M.D.; curator, Joseph W. England; editor, Henry Kraemer; librarian, Katharine E. Nagle; trustees for three years: Joseph P. Remington, C. Stanley French, George B. Evans; Publication Committee: Samuel P. Sadtler, Henry Kraemer, Joseph P. Remington, Joseph W. England, Martin I. Wilbert, Charles H. La Wall, and John K. Thum; Committee on Pharmaceutical Meetings: Henry Kraemer, Joseph P. Remington, C. B. Lowe, George B. Weidemann, and E. H. Hessler.

The President declared the above duly elected.

The President made the following appointments:

Committee on By-Laws: George M. Beringer, Joseph W. England, and C. A. Weidemann.

Delegates to the Pennsylvania Pharmaceutical Association: C. B. Lowe, Joseph P. Remington, F. P. Stroup, O. W. Osterlund, William E. Lee, Charles H. La Wall, and E. Fullerton Cook.

Delegates to New Jersey Pharmaceutical Association: Henry Kraemer, George M. Beringer, C. B. Lowe, Charles H. La Wall, and H. P. Thorn.

Delegates to Delaware Pharmaceutical Association: A. W. Miller, M.D., C. B. Lowe, and H. J. Watson.

The President announced the death of David H. Ross on January 26, 1914. He joined the College in 1888.

William M. Morrison presented an old scale and two cases of instruments originally owned by Dr. Stott, who died in 1837. The thanks of the College were tendered the donor.

C. A. WEIDEMANN, M.D.,
Recording Secretary.

ABSTRACTS FROM THE MINUTES OF THE BOARD OF TRUSTEES.

December 2, 1913.—Sixteen members present.

Committee on Library reported total number of books accessioned to date 5449. A number of books were purchased during the month and the Library was used by 154 persons.

A communication from the Board of Public Education was read, recommending that Miss Florence McGarrity be awarded a scholarship; and, on motion, the recommendation was approved.

An application for active membership was received from a graduate of the 1913 class, now a resident of China, and, as usual, it was referred to the Committee on Membership.

The Treasurer reported that on November 8th Mrs. Anna Shinn Maier sent her check for $2000 to establish a scholarship in memory of her father, James T. Shinn, the income from said amount to be devoted for scholarship purposes. On motion, it was voted that the Treasurer convey the thanks of the College to Mrs. Maier.

January 6, 1914.—Fifteen members present.

Committee on Property reported the change from white to green

shades in the electric light over the lecture table in the Materia Medica room.

A petition signed by 75 per cent. of the students relative to the establishment of a lunch room in the College building was submitted by the Property Committee. The Dean explained in detail the reasons that prompted the presenting of the petition by the students, and advocated the adoption of a plan complying with their request. After some discussion it was moved that the Board approve the plan if the Committee on Property found that same could be put in operation without the College being compelled to assume any responsibility. It was so ordered.

Committee on Library reported 476 books accessioned and shelf-listed during the month. A number of books had been donated and 190 persons had used the Library during the month.

Committee on Accounts and Audit reported they had examined the accounts of the Treasurer, Registrar, and the AMERICAN JOURNAL OF PHARMACY, and found them correct.

Committee on Announcement reported the publication of the December issue of the Bulletin, that Pharmacy Talk No. 1 had been sent out, and that they had in preparation a series of 8 "Talks"—one to be issued each month.

The Corresponding Secretary of the College read several letters from those who were recently elected to Honorary Membership in the College.

The Committee on Membership having reported favorably on the application of Mr. Job Fong, of Canton, China, for active membership, a ballot was taken and he was unanimously elected.

February 3, 1914.—Fourteen members present.

Committee on Property reported that inquiries had been made and it was found to be possible to make arrangements with a caterer to serve a light lunch in the College building for the accommodation of the students. On motion, the matter was referred to the Committee on Property with power to act.

Committee on Library reported that 454 books were accessioned during the month, making a total of 6378 books ready to be catalogued. The Library was consulted by 143 persons.

Committee on Instruction reported progress concerning matters that they had had under consideration.

The Chair announced that Dr. P. S. Stout had been requested to present a report of the Alumni Special Committee having in

charge the Centennial Fund, and asked that the regular order of business be suspended. This being agreed to, Dr. Stout was introduced and presented a detailed report of what had been done up to this time. The main object of the movement is to obtain by subscription and bequest, as may be most acceptable to the donor, a fund of $500,000 or more, to be devoted to improvements—location, building, equipment, etc., and to the establishment of an endowment for the College. The action of the committee was endorsed, and the Board gave assurance of furthering the movement in every way possible.

Committee on Examinations reported they had been engaged for several months in formulating a set of rules for regulating the conduct of examinations in the College. A number of recommendations were submitted and extended discussion followed. As this was an important matter, it was voted that further consideration of the subject be deferred to an adjourned meeting to be held February 9th.

The Dean presented the form of certificate which the Board had some months before referred to a Special Committee for consideration, covering special branches of study. The form met with approval, and it was voted that certificates be finished in accordance with the outlines proposed.

An application for active membership was received and referred to the appropriate committee.

February 9, 1914.—Eleven members present.

This meeting was called to give further consideration to the report of the Committee on Examinations. After an extended discussion, participated in by many of the members, action was deferred.

PRESIDENT'S ADDRESS.[1]

To the Members of the Philadelphia College of Pharmacy:

Your President has pleasure in submitting at this time, in accordance with his established practice, a brief summary of matters of general interest relating to your institution.

The College buildings at the present time are in good condition. The walls and ceiling of the library have been painted, the floor covered with a cork carpet, and new chairs provided. The walls of the back stairway have been coated with a light-colored paint, which has proven of advantage in brightening up this portion of

[1] In abstract.

the building. Alterations were made in the third-floor Microscopical Laboratory, giving greater facilities for the revised and expanded course in Bacteriology, which is now an obligatory course in charge of Prof. John A. Roddy. Changes have also been made in Alumni Hall for the benefit of the classes in Microscopy.

Following the approval of the Board of Trustees of a petition signed by a number of the students, asking that a lunch-room be established, a lunch counter was started a few weeks ago and is being continued with increasing success. The lunches furnished are substantial and wholesome, and from the patronage received it would appear that the students in general appreciate the innovation. The Property Committee will, no doubt, find it necessary, in the near future, to enlarge the facilities for this purpose, as the present accommodations are not equal to the demand.

The total number of students in attendance at the College at this time is 434, an increase of fourteen over last year. Of the number mentioned, 145 are first-year students, 109 second-year students, 141 third-year students, 38 special chemistry students, and 1 student taking the Food and Drug course. There were 168 first-year matriculants—167 regulars and 1 special. Of this number, 1 student is deceased and 22 are not attending. The second-year matriculants numbered 113—112 regulars and 1 special. Of this number, 4 are not attending. There were 124 regular third-year matriculants and 18 students remaining from class of 1912–13. Of the total of 142 third-year students, 1 is not attending.

Of those seeking admittance to the College at the beginning of the fall term, 29 applicants were not able to furnish satisfactory entrance credentials. These were given the privilege of remaining at the College and repeating the first-year work during 1914–15, in the meantime being expected to qualify. A few of the number have availed themselves of this privilege, but of these only four are attending at the present time, and under the circumstances are not listed as students.

In the department of Analytical Chemistry, 13 first-year, 28 second-year, and 35 third-year students have been doing special work. Of the number of third-year students mentioned, 9 are doing thesis work. Twenty-five students are taking the special laboratory course in Bacteriology; of this number, 7 are specials and 18 regulars. Fourteen of the special Chemistry students are availing themselves of the special course in Microscopy; and 10

students are doing special work in the Microscopical Laboratory, in connection with their theses.

The work in the Department of Pharmacy for the course of 1914–1915 is being successfully carried on.

The recording of the attendance, as now required by the State Pharmaceutical Board, has been of considerable value, and resulted in a higher grade of scholarship being attained by the classes.

The extra lectures on pharmaceutical subjects given during the college courses have been of material value and more largely attended.

The course in Commercial Training, under the control of the Department of Pharmacy, and for which the students are not charged, has been greatly increased; the number of hours devoted to this branch has been doubled since last year. Illustrative material is fully shown, bookkeeping methods are compulsory, and students are now required to keep an individual set of books and submit them for examination.

The Department of Botany and Pharmacognosy has given evidence of considerable advancement during the past year. A specialized course in Microscopy has been developed, giving the special chemistry students enlarged opportunities for increasing their efficiency and broadening their powers as analysts. The course comprises a series of laboratory periods on Saturday mornings and includes a wide range of topics, namely, the study of drugs, foods, and technical products with their deterioration and adulteration. The large number of specimens bearing upon this work, which your Professor of Botany and Pharmacognosy and his assistants have been diligently collecting for a number of years, is now being brought into practical use, and is proving of great advantage.

It is of interest to note the increasing demand among agricultural experiment stations and the government laboratories for pharmacognocists or thoroughly trained analysts; and as microscopical courses are not, as a rule, included with chemical courses given in this country, the Philadelphia College of Pharmacy, in the establishment of such a course, will undoubtedly be enabled to prepare students of chemistry for a broader knowledge and a deeper understanding of the intricacies of the work they have elected, thus extending the educational prestige of the College.

The greenhouse and roof garden continue to furnish the students in Botany and Pharmacognosy facilities for growing plants and conducting special investigations.

In the Department of Materia Medica the Physiological assay of drugs has been given increased attention, with good results. Your Medical Examiner reports that the physical examination of your students is somewhat hampered by lack of sufficient light. It may, therefore, be necessary for your Committee on Property to install a special light for this purpose in the near future.

On Thursday evening, May 22, 1913, the 92nd Annual Commencement exercises of your College were held in the Academy of Music. The graduating class numbered 123, representing 22 States of the Union, District of Columbia, Canada, China, and Russia.

During the past year the College has received from Mrs. Anna Shinn Maier, daughter of your late treasurer, James T. Shinn, a sum sufficient to convert the Shinn Memorial into a scholarship.

The Pennsylvania Scholarship Fund of $2500 is nearing completion; $2200 has been collected.

There are at present 148 active members of your College, and 13 associate members. During the year 6 active members and 1 associate member were elected. The resignation of one active member was received; and your President regrets to report the death of three of your active members during the year, as follows:

John W. Ridpath, May 8, 1913. Joined the College in 1888.

Evan T. Ellis, September 29, 1913. Joined the College in 1852.

David H. Ross, January 26, 1914. Joined the College in 1879.

It is of interest to note that Evan T. Ellis was the oldest member of the College.

It is thought desirable by your President to bring to your attention the fact that the Department of Public Safety of Philadelphia, recognizing the danger incident to smoking in buildings where people are assembled in numbers on various floors, deemed it necessary to send a communication to your College, reading as follows:

MR. HOWARD B. FRENCH, *President,*
Philadelphia College of Pharmacy,
145 No. 10th Street,
Philadelphia.

DEAR SIR:

Complaint has been made to this Bureau of the promiscuous smoking of cigarettes and cigars in the building of the College of Pharmacy.

The Fire Marshal has made an inspection of the complaint and considers it of vital importance that the practice be discontinued at once.

I therefore request that proper notices be placed in all parts of the building where there are no tile or cement floors, in order that those offending may have knowledge of the fact that it is in violation of the Act of Assembly.

I would appreciate it if you would give this the publicity it deserves.

Yours very truly,
(Signed) GEO. D. PORTER,
Director.

The body of this communication has been printed and prominently displayed throughout your buildings; and it is earnestly hoped that students in the College will respect said notice by discontinuing the practice of smoking in the portions of the buildings where there are no tile or cement floors, and that arbitrary measures to enforce the order may not be found necessary.

Your President wishes to call attention to the fact that on the 21st of March, 1921, the College will have attained the one hundredth anniversary of its existence. This is but seven years away, and your President desires to urge upon all members of the College the desirability of collecting and placing in possession of the College any historical matters they may have or may be able to obtain. He would suggest that old prescription labels and labels referring to specific preparations could be readily collected from time to time from many of the old drug stores, and would prove of much interest. He also hopes that a strenuous effort may be made to collect as many of the old-time appliances as possible. It is the earnest hope of your President that when celebrating the 100th birthday of the College there may be an historical exhibition at that time that will not only attract the attention and interest of the pharmacists throughout the country, but of members of the medical and allied professions.

In closing, your President desires to express appreciation to those of the officers and faculty who have so heartily coöperated with him during the past year; and to those who have not been in full accord with his views, he wishes to express the hope that all personal feelings may be put aside and that a united effort may be made to continue the prosperity and advancement of this institution, which is dear to the hearts of all those associated with it.

HOWARD B. FRENCH.

March 30, 1914.

THE VITAMINES.[1]

The Recognition of Essential Constituents of the Diet Hitherto Unclassified—Deficiency Diseases.

By Percy G. Stiles.

If a physiologist is asked what are the requisites of a normal diet he will probably reply somewhat as follows: First, it must represent an adequate quantity of available potential energy, not less than 2,000 calories for the average human adult. Second, it must contain protein (nitrogenous) food sufficient to compensate for the unavoidable daily loss of similar material from the body. Third, it must be palatable and digestible, making due allowance for personal idiosyncrasy. He will very probably content himself with these three postulates.

If the inquiry is pressed the man of science may recollect that another necessary condition of successful nutrition is a proper supply of the inorganic or mineral elements in sufficiently varied assortment. The tissues cannot be developed or maintained without chlorides, phosphates, and other saline contributions. The need for substances of this class is more urgent during the period of growth than later, but it always continues to exist. A similar statement may be made with reference to the protein of the ration; this, too, must be furnished in relative abundance and varied form during the growth of the subject and may be reduced when full stature has been reached. Mendel has shown that kind as well as quantity must be considered when protein is chosen for experimental nutrition of an animal. Proteins from certain sources suffice for maintenance only and not to minister to growth.

With the accumulation of physiological data during the past few years it has become increasingly apparent that there may be criteria for the adequacy of a diet not included in the list just given. There are now known to be organic compounds other than proteins, small quantities of which are absolutely essential to normal growth and even to continued health in the adult condition. The name of Vitamines has been proposed for all such substances. The word is well chosen in view of its root-meaning; an amine is a nitrogenous compound of a certain type and a vitamine is obviously such a

[1] Reprinted from *Science Conspectus*, Vol. IV, 1914, pp. 10-13.

compound with the added distinction of being necessary to life. Casimir Funk of London has been one of the foremost contributors to the development of this conception and a valuable summary of his own work and his judgment of the work of others may be found in the *Ergebnisse der Physiologie,* Vol. XIII, pp. 124–205. (Wiesbaden, 1913.) This article is the chief source of the present abstract.

A class of serious disorders has long been known in which failure of nutrition could be named as the cardinal fact in the case and in which it has somewhat vaguely been assumed that the diet must be at fault. The most familiar disturbance of this class, at least to the general reader, has probably been scurvy. The chronicles of exploring expeditions in polar regions have contained many harrowing accounts of the ravages of this disease. It has usually been associated with the consumption of a monotonous ration, deficient in fresh vegetables and often containing a great deal of salted or canned food. Certain supplementary articles of diet, such as onions, limes, and lemons, have been credited with some power to ward off or at least to mitigate the trouble and they have been spoken of as antiscorbutics.

The victims of scurvy suffer from severe prostration, loosening of the teeth, intense soreness of the gums, friability of the bones, and a tendency to hæmorrhage partly due to a loss of the coagulating property of the blood. Those who have read the classic journals of Doctor Kane will recall the distressing situation on board his ship at the end of the Arctic winter and the commander's device to cheer his helpless men in the forecastle by setting up a mirror to bring into their midst the first sunbeam from the southern horizon. Scurvy has become less common with better supplies of food available for such parties, but it has been noted within a very few years.

Another disorder which has lately attracted much attention is beri-beri. It has its recognized centre in the East, particularly in Japan, China, Indo-China, and the Philippines. Its occurrence in Newfoundland has recently been reported. Those who suffer from beri-beri are usually the very poor and, in the Orient at least, they are people who live chiefly upon rice. In Japan the disease has been nearly eliminated from the army and navy by providing more liberal and varied rations. The symptoms are complex, but they are in general such as can be referred to the impairment of the nerves, which is known to be the most prominent physical change. There is a period of declining weight and strength and this is followed by

the development of a "multiple neuritis" with partial paralysis in both the motor and the sensory realms.

Various theories have been held with regard to beri-beri. It has been believed to be an infectious disease because it so often affects a large number of people who are closely associated, as in a prison, a ship, or a laborers' camp. The fact was formerly overlooked that such companies share the same diet and that their trouble may well be due to that source. This is now accepted as proved. But when the decision is reached that something must be wrong with the food there are still two possible views to be considered. Is the diet positively poisonous or is it merely insufficient? This question has been asked both with reference to scurvy and to beri-beri. It is not easy to answer it in such a way as to meet all objections. Nevertheless, the tendency is toward the conclusion that it is the inadequacy rather than the toxic nature of the food which is to be held responsible in these and perhaps in other cases.

It is proposed to call such failures of nutrition "deficiency diseases." It is assumed that the lack is of one or more of the specific substances already termed vitamines. The evidence in support of such a conception is especially convincing in the case of beri-beri. As long ago as 1897 it was discovered that rice which has been "polished"—that is, deprived of its pericarp or immediate husk—has a tendency to induce beri-beri and that the inclusion of the pericarp makes it entirely wholesome. It has been possible to confirm this in a striking manner by experiments on birds. If a fowl or a pigeon is restricted to polished rice as a diet it soon refuses to eat. If forced feeding is then resorted to it soon becomes pitiably weak and cannot long survive. The partial feeding is thus as surely destructive as absolute starvation. Post-mortem study of such birds shows marked degeneration of the nerves. The service of the pericarp may be conceived of in either of two ways. The polished rice may contain an active poison for which the husk provides a natural antidote. The alternative is that the pericarp furnishes a necessary constituent of the nerve tissue, a vitamine, for want of which the nerve-fibres deteriorate. How hard it is to choose between these two views has already been suggested.

Funk has been successful in his patient endeavor to isolate the vitamine the lack of which causes beri-beri. He has obtained from the pericarp of rice a number of fractions, only one of which has the remedial property. This appears to be a definite organic

body to which a formula can be assigned. It contains nitrogen but not phosphorus, an element which earlier workers had believed to be concerned. The vitamine can be separated from other foods than rice. Various animal tissues yield it and so do certain vegetables. Any kind of food which contains the vitamine may be used to supplement a ration of polished rice with the result that it becomes sufficient for the maintenance of the animal. Yolk of egg and yeast are said to have the curative power in the highest degree.

It is interesting to follow Funk's conjectures as to the systemic effects of the withholding of the invaluable vitamine. We know that in starvation the organs which cannot be spared are sustained at the expense of others. The heart and the nervous system have been found to keep their full weight to the last while tissues which are less necessary to the continuance of life are greatly reduced. Even the bones are levied upon to the extent of one-sixth of their mass. We may expect to see the same principle illustrated in the partial starvation which is at the root of any deficiency disease.

So in beri-beri it may be supposed that the vitamine which is absolutely essential to the normal nervous system is not at first confined to that part of the body. The feeding experiments have given evidence that it is present in the muscles though rather scantily. It is to be expected that in the event of failure of a supply direct from the diet the muscles will be made to surrender their store of the vitamine to replace that which has been destroyed in the nervous tissues. If we are to think that the vitamine is essential to the muscles as well as to the nerves we shall anticipate that its withdrawal will result in a disintegration of the muscle protoplasm quite out of proportion to the small amount of vitamine yielded to the preferred creditor. So for a while there will be loss of weight and strength but no marked nervous symptoms because the nerves are being kept in condition at the cost of a remorseless sacrifice of the other tissues. When the internal supply ceases to be sufficient the acute nervous effects are at once developed.

It is the opinion of Funk that both beri-beri and scurvy are prevented by the liberal use of potatoes. Before this vegetable was introduced into Europe there were severe epidemics which are believed to have been outbreaks of scurvy. The suggestion that the potato should now be added to the food-supply of the eastern countries in which beri-beri is prevalent seems a wise one. But the fact is to be emphasized that almost any diet is free from ob-

jection if it is reasonably varied. It is where poverty or some other compulsion is operative that nutritional disasters are likely.

The condition of the body in scurvy is quite different from that in beri-beri and the missing compounds are probably somewhat unlike. Some articles of diet may protect against both; some may be specific for only one. Allied with scurvy are the disorders called ship beri-beri, infantile scurvy (Barlow's disease), and the experimental scurvies which can be produced in animals by limiting the intake to a few foods. Still other pathological states may be found to have a more or less similar basis. An attempt has been made to justify the claim that pellagra is a deficiency disease, but this is strongly contested. Abnormalities of early development such as rachitis (rickets) and, perhaps, later perversions of growth such as cancer may be connected with the lack of certain chemical constituents in the income of the body. At this point it may be in order to say that the diet itself may conceivably be ideal and yet there may be a failure to utilize the vitamines offered either because of a failure to absorb them or because of the premature decomposition in the alimentary tract.

A few years ago Crichton-Browne, an English authority, in passing an unfavorable judgment upon the dietetic standards of Chittenden and others called attention to the fact that the diet approved by them seemed to correspond closely with that of the very poor. The comparison was based upon fuel value and protein content. It is now possible to modify the statement that the two are precisely equivalent. The low diet of the New Haven school is an inclusive one, while that of the poor is of limited variety. A supply of the requisite minor bodies—vitamines, if we adopt the term—is much more surely to be relied on in the first case.

Bunge, the Austrian physiologist, pointed out in 1901 that sugar is an unnatural food, in that it has been refined to the exclusion of all compounds but saccharose. Foods which are not deliberately prepared by industrial or domestic processes are always mixtures, however much one constituent may predominate. The teaching of Sylvester Graham in the first half of the nineteenth century that the foods offered by nature should not be separated into their ingredients but taken in their entirety is frequently reëchoed in our own day. In the light of studies like those of Funk it is apparent that there is a certain foundation for the idea that foods may be "denatured" either by discarding valuable fractions or by modes

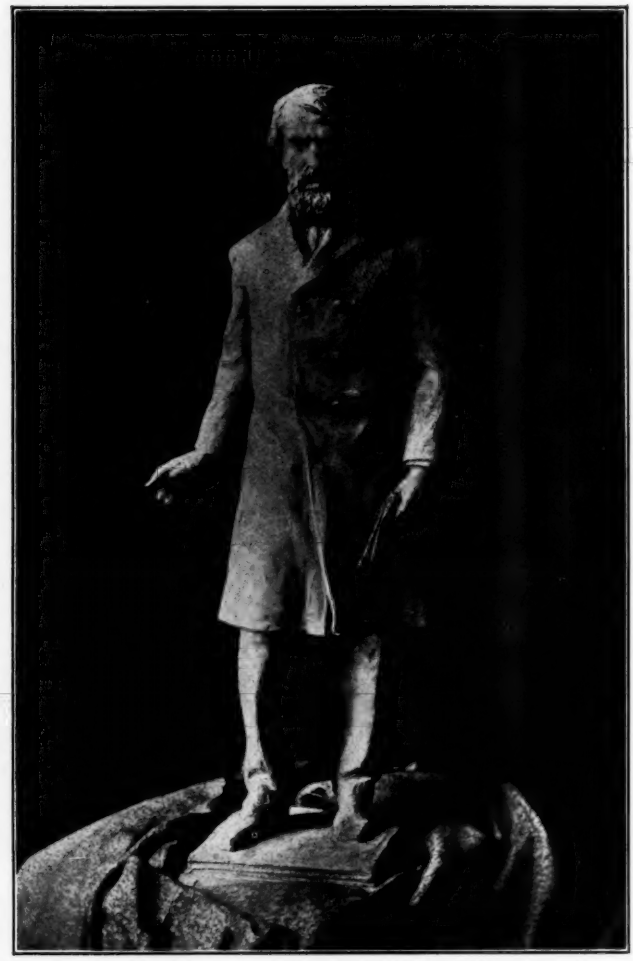
of preparation which destroy essential compounds. The fear that disturbances of nutrition from such causes threaten the American people as a whole may be dismissed, but it is interesting to have a new insight into a matter which under certain conditions becomes of pressing importance.

PHARMACEUTICAL MEETING.

At the third Pharmaceutical Meeting held February 20th, Mr. A. K. Lobeck spoke on "A Roughing Trip Across the Continent," showing about 150 colored slides. While the subject may have seemed remotely connected with pharmacy, yet, as Mr. Poley very well brought out in his remarks afterward, anything which will attract the pharmacist's attention to out-of-door life will be a benefit to him and tend to draw him away from his confined state of existence.

Mr. Lobeck attempted throughout the story of the trip to interpret the natural scenery of the country. The origin of Niagara Falls, the fact that they are receding at the rate of 5 feet per year, the geological reason for the forms observed in the Garden of the Gods, and the explanation of the scenery around Horse Shoe Curve were some of the things dwelt upon. A summary of the trip was given showing in detail the distribution of the expenses and giving the average of expenses for each day. Exclusive of railroad fares it was shown that the average cost per day was 88 cents, this low average being accounted for by the fact that during the trip of 63 days, 27 days were spent camping or on ranches, either working or under more hospitable circumstances.

WHAT IS SLEEP? In an article on "Sleep" Dr. Boris Sidis says: "Sleep is not a disease, not a pathological process due to the accumulation of toxic products in the brain or in the system generally. Sleep is not an abnormal condition, it is a normal state. Like the waking states, sleep states are part and parcel of the life-existence of the individual. Waking and sleeping are intimately related—they are two different manifestations of one and the same life-process—one is as normal and healthy as the other."



THE PROCTER MONUMENT. PHOTOGRAPH OF MODEL OF THE BRONZE STATUE, DESIGNED BY EDWARD BERGE, AND TO BE ERECTED IN WASHINGTON, D. C., WHEN COMPLETED.